L2 ANSWER 1 OF 9 MEDLINE
TI A study of modified betaines as cryoprotective additives.
AU Lloyd A W; Olliff C J; Rutt K J
SO JOURNAL OF PHARMACY AND PHARMACOLOGY, (1994 Sep) 46 (9) 704-7.
Journal code: JNR. ISSN: 0022-3573.
AB Glycinebetaine and N-modified betaines have been previously shown to be effective at reducing leakage from liposomes on freeze-thaw procedures. This study involved the preparation of a series of other modified betaines and the comparison of their abilities to reduce leakage from frozen multilamellar liposomes. All the compounds investigated, with the exception of the octyl ester of betaine, reduced the degree of leakage on freezing and thawing with additive concentrations up to 0.6 M. The betaine esters were less effective than betaine as cryoprotective additives and caused an increase in the leakage from unfrozen liposomes. Taurinebetaine, a **sulphobetaine**, was also less effective at reducing leakage on freezing than betaine and again increased leakage from unfrozen liposomes. Increasing the number of methylene groups between the carboxylate group and the nitrogen improved the ability to reduce leakage, particularly at

L2 ANSWER 3 OF 9 MEDLINE

TI Solubilisation effect of Nonidet P-40, triton X-100 and CHAPS in the detection of MHC-like glycoproteins.

AU Labeta M O; Fernandez N; Festenstein H

SO JOURNAL OF IMMUNOLOGICAL METHODS, (1988 Aug 9) 112 (1) 133-8. Journal code: IFE. ISSN: 0022-1759.

AB We have analysed the differential solubilisation effect of three detergents on cell-membrane histocompatibility glycoproteins. Two nonionic detergents (Nonidet P-40 and Triton X-100) which are extensively used in the extraction of MHC proteins and a zwitterionic detergent (CHAPS) which is **sulphobetaine** derivative of cholic acid were used. An AKR (H-2k) derived spontaneous leukaemic cell line--424--was used as the experimental model. In this tumour cell line a class I-like antigen is expressed but not directly detected by cell-binding radioimmunoassay or immunoprecipitation from NP-40 or Triton X-100 solubilised glycoproteins. However, 46 kDa and 12 kDa bands consistent with the classical H-2 class I pattern were seen by SDS-PAGE after immunoprecipitation with the 34.5.8 anti-H-2Dd MoAb using CHAPS solubilised 424 glycoproteins. The H-2Dd-reactive molecule appears to be associated with at least one of the syngeneic class I specificities (H-2Kk, H-2Dk) and not accessible to react with the specific anti H-2Dd MoAb. The detergents NP-40 and Triton X-100 appear to be less efficient than CHAPS in breaking protein-protein interactions. This property of CHAPS permitted the adequate solubilisation of the novel antigen and its direct detection. The results of this study suggest that the alternative use of a non-denaturing zwitterionic detergent may contribute to the detection and characterisation of MHC-related, membrane-bound proteins of tumours and normal cells.

L5 ANSWER 10 OF 73 MEDLINE

TI Subcellular colocalization of the cellular and scrapie prion proteins in caveolae-like membranous domains.

AU Vey M; Pilkuhn S; Wille H; Nixon R; DeArmond S J; Smart E J; Anderson R G;
Taraboulos A; Prusiner S B

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Dec 10) 93 (25) 14945-9.
Journal code: PV3. ISSN: 0027-8424.

AB Results of transgenetic studies argue that the scrapie isoform of the prion protein (PrPSc) interacts with the substrate cellular **PrP** (PrPC) during conversion into nascent PrPSc. While PrPSc appears to accumulate primarily in lysosomes, caveolae-like domains (CLDs) have been suggested to be the site where PrPC is converted into PrPSc. We report herein that CLDs isolated from scrapie-infected neuroblastoma (ScN2a) cells contain PrPC and PrPSc. After lysis of ScN2a cells in ice-cold Triton X-100, both **PrP** isoforms and an N-terminally truncated form of PrPC (PrPC-II) were found concentrated in detergent-insoluble complexes resembling CLDs that were isolated by flotation in sucrose gradients. Similar results were obtained when CLDs were purified from plasma membranes by sonication and gradient **centrifugation**; with this procedure no detergents are used, which minimizes artifacts that might arise from redistribution of proteins among subcellular fractions. The caveolar markers ganglioside GM1 and H-ras were found concentrated in the CLD fractions. When plasma membrane proteins were labeled with the impermeant reagent sulfo-N-hydroxysuccinimide-biotin, both PrPC and PrPSc were found biotinylated in CLD fractions. Similar results on the colocalization of PrPC and PrPSc were obtained when CLDs were isolated from Syrian hamster brains. Our findings demonstrate that both PrPC and PrPSc are present in CLDs and, thus, support the hypothesis that the PrPSc formation occurs within this subcellular compartment.

L5 ANSWER 11 OF 73 MEDLINE

TI The association between PrP and infectivity in scrapie and BSE infected mouse brain.

AU Somerville R A; Dunn A J

SO ARCHIVES OF VIROLOGY, (1996) 141 (2) 275-89.
Journal code: 8L7. ISSN: 0304-8608.

AB The structure of the scrapie agent remains unknown. However, scrapie infectivity tends to co-sediment with an infection specific fraction of the glycoprotein **PrP** (PrPSc) under conditions which solubilise the normal form of this protein (PrPc); accordingly, **PrP** has been proposed as a candidate component of the agent. To investigate this further we have been examining a new scrapie-related murine model in conjunction with established scrapie models. A bovine spongiform encephalopathy (BSE) derived murine model has short incubation periods, high infectivity titre and low amounts of **PrP** deposited in the brain. A membrane fraction from scrapie/BSE infected brain is solubilised with Sarkosyl at pH > or = 9.0. Most **PrP** is also solubilised. In models of the disease with little deposition of the **PrP** in the brain, this solubilisation step is particularly effective in reducing the amounts of **PrP** sedimented from brain extracts. Gradient **centrifugation** of the sedimented fraction shows further separation of infectivity and the residual **PrP**. It is concluded that at least some PrPSc in the brain need not be associated directly with infectious agents but is deposited in brain solely as a pathological product of infection. However, a residual sedimentable fraction contains

L5 ANSWER 12 OF 73 MEDLINE

TI Disruption of prion rods generates 10-nm spherical particles having high alpha-helical content and lacking scrapie infectivity.

AU Riesner D; Kellings K; Post K; Wille H; Serban H; Groth D; Baldwin M A; Prusiner S B

SO JOURNAL OF VIROLOGY, (1996 Mar) 70 (3) 1714-22.
Journal code: KCV. ISSN: 0022-538X.

AB An abnormal isoform of the prion protein (**PrP**) designated PrPSc is the major, or possibly the only, component of infectious prions. Structural studies of PrPSc have been impeded by its lack of solubility under conditions in which infectivity is retained. Among the many detergents examined, only treatment with the ionic detergent sodium dodecyl sulfate (SDS) or Sarkosyl followed by sonication dispersed prion rods which are composed of **PrP** 27-30, an N-terminally truncated form of PrPSc. After ultracentrifugation at 100,000 x g for 1 h, approximately 30% of the **PrP** 27-30 and scrapie infectivity were found in the supernatant, which was fractionated by sedimentation through 5 to 20% sucrose gradients. Near the top of the gradient, spherical particles with an observed sedimentation coefficient of approximately 6S, approximately 10 mm in diameter and composed of four to six **PrP** 27-30 molecules, were found. The spheres could be digested with proteinase K and exhibited little, if any, scrapie infectivity. When the prion rods were disrupted in SDS and the entire sample was fractionated by sucrose gradient **centrifugation**, a lipid-rich fraction at the meniscus composed of fragments of rods and heterogeneous particles containing high levels of prion infectivity was found. Fractions adjacent to the meniscus also contained spherical particles. Circular dichroism of the spheres revealed 60% alpha-helical content; addition of 25% acetonitrile induced aggregates high in beta sheet but remaining devoid of infectivity. Although the highly purified spherical oligomers of **PrP** 27-30 lack infectivity, they may provide an excellent substrate for determining conditions of renaturation under which prion particles regain infectivity.

L7 ANSWER 4 OF 14 MEDLINE

TI Subcellular colocalization of the cellular and scrapie prion proteins in caveolae-like membranous domains.

AU Vey M; Pilkuhn S; Wille H; Nixon R; DeArmond S J; Smart E J; Anderson R G;
Taraboulos A; Prusiner S B

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Dec 10) 93 (25) 14945-9.
Journal code: PV3. ISSN: 0027-8424.

AB Results of transgenetic studies argue that the scrapie isoform of the prion protein (PrPSc) interacts with the substrate cellular **PrP** (PrPC) during conversion into nascent PrPSc. While PrPSc appears to accumulate primarily in lysosomes, caveolae-like domains (CLDs) have been suggested to be the site where PrPC is converted into PrPSc. We report herein that CLDs isolated from scrapie-infected neuroblastoma (ScN2a) cells contain PrPC and PrPSc. After lysis of ScN2a cells in ice-cold Triton X-100, both **PrP** isoforms and an N-terminally truncated form of PrPC (PrPC-II) were found concentrated in detergent-insoluble complexes resembling CLDs that were isolated by flotation in **sucrose** gradients. Similar results were obtained when CLDs were purified from plasma membranes by sonication and gradient centrifugation; with this procedure no detergents are used, which minimizes artifacts that might arise from redistribution of proteins among subcellular fractions. The caveolar markers ganglioside GM1 and H-ras were found concentrated in the CLD fractions. When plasma membrane proteins were labeled with the impermeant reagent sulfo-N-hydroxysuccinimide-biotin, both PrPC and PrPSc were found biotinylated in CLD fractions. Similar results on the colocalization of PrPC and PrPSc were obtained when CLDs were isolated from Syrian hamster brains. Our findings demonstrate that both PrPC and PrPSc are present in CLDs and, thus, support the hypothesis that the PrPSc

NSWER 6 OF 14 MEDLINE

TI Disruption of prion rods generates 10-nm spherical particles having high alpha-helical content and lacking scrapie infectivity.

AU Riesner D; Kellings K; Post K; Wille H; Serban H; Groth D; Baldwin M A; Prusiner S B

SO JOURNAL OF VIROLOGY, (1996 Mar) 70 (3) 1714-22.
Journal code: KCV. ISSN: 0022-538X.

AB An abnormal isoform of the prion protein (**PrP**) designated PrPSc is the major, or possibly the only, component of infectious prions. Structural studies of PrPSc have been impeded by its lack of solubility under conditions in which infectivity is retained. Among the many detergents examined, only treatment with the ionic detergent sodium dodecyl sulfate (SDS) or Sarkosyl followed by sonication dispersed prion rods which are composed of **PrP** 27-30, an N-terminally truncated form of PrPSc. After ultracentrifugation at 100,000 x g for 1 h, approximately 30% of the **PrP** 27-30 and scrapie infectivity were found in the supernatant, which was fractionated by sedimentation through 5 to 20% **sucrose** gradients. Near the top of the gradient, spherical particles with an observed sedimentation coefficient of approximately 6S, approximately 10 mm in diameter and composed of four to six **PrP** 27-30 molecules, were found. The spheres could be digested with proteinase K and exhibited little, if any, scrapie infectivity. When the prion rods were disrupted in SDS and the entire sample was fractionated by **sucrose** gradient centrifugation, a lipid-rich fraction at the meniscus composed of fragments of rods and heterogeneous particles containing high levels of prion infectivity was found. Fractions adjacent to the meniscus also contained spherical particles. Circular dichroism of the spheres revealed 60% alpha-helical content; addition of 25% acetonitrile induced aggregates high in beta sheet but remaining devoid of infectivity. Although the highly purified spherical oligomers of **PrP** 27-30 lack infectivity, they may provide an excellent substrate for determining conditions of renaturation under which prion particles regain infectivity.

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ANSWER 7 OF 14 MEDLINE

TI Characterization of PrP binding proteins.

AU Oesch B

SO PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON. SERIES B: BIOLOGICAL SCIENCES, (1994 Mar 29) 343 (1306) 443-5.
Journal code: P5Z. ISSN: 0962-8436.

AB Prions cause spongiform degeneration in various mammalian species. The scrapie prion protein (PrPSc) is part of the infectious particle and may mediate infection and spreading of the disease in the brain. It was therefore of interest to purify and analyse **PrP** ligands (Plis). Plis were identified on ligand blots using either intact **PrP** or peptides corresponding to the central portion of **PrP**. Here, characterization of a 110 and a 125 kDa Pli is reported. Both Plis were found in total membrane fractions and could be extracted with carbonate indicating that they are not integral membrane proteins. On **sucrose** gradients both **PrP** ligands sedimented with high density

ER 8 OF 14 MEDLINE

TI Binding of the protease-sensitive form of PrP (prion protein) to sulfated glycosaminoglycan and congo red [corrected] [published erratum appears in J Virol 1994 Jun;68(6):4107].

AU Caughey B; Brown K; Raymond G J; Katzenstein G E; Thresher W

SO JOURNAL OF VIROLOGY, (1994 Apr) 68 (4) 2135-41.
Journal code: KCV. ISSN: 0022-538X.

AB Congo red and certain sulfated glycans are potent inhibitors of protease-resistant **PrP** accumulation in scrapie-infected cells. One hypothesis is that these inhibitors act by blocking the association between protease-resistant **PrP** and sulfated glycosaminoglycans or proteoglycans (e.g., heparan sulfate proteoglycan) that is observed in amyloid plaques of scrapie-infected brain tissue. Accordingly, we have investigated whether the apparent precursor of protease-resistant **PrP**, protease-sensitive **PrP**, binds to Congo red and heparin, a highly sulfated glycosaminoglycan with an inhibitory potency like that of heparan sulfate. Protease-sensitive **PrP** released from the surface of mouse neuroblastoma cells bound to heparin-agarose and Congo red-glass beads. **Sucrose** density gradient fractionation provided evidence that at least some of the **PrP** capable of binding heparin-agarose was monomeric. Free Congo red blocked **PrP** binding to heparin and vice versa, suggesting that these ligands share a common binding site. The relative efficacies of pentosan polysulfate, Congo red, heparin, and chondroitin sulfate in blocking **PrP** binding to heparin-agarose corresponded with their previously demonstrated potencies in inhibiting protease-resistant **PrP** accumulation. These results are consistent with the idea that sulfated glycans and Congo red inhibit protease-resistant **PrP** accumulation by interfering with the interaction of **PrP** with an endogenous glycosaminoglycan or proteoglycan.

L7 ANSWER 12 OF 14 MEDLINE
TI Nuclease-resistant polyadenylated RNAs of significant size are detected by
PCR in highly purified Creutzfeldt-Jakob disease preparations.
AU Akowitz A; Sklaviadis T; Manuelidis E E; Manuelidis L
SO MICROBIAL PATHOGENESIS, (1990 Jul) 9 (1) 33-45.
Journal code: MIC. ISSN: 0882-4010.
AB The molecular nature of the 'unconventional viruses' that cause slow, progressive brain deterioration is still poorly understood. As part of a reinvestigation of potential agent-specific nucleic acids, we developed a protocol for enriching agent-specific sequences. This protocol uses extensive micrococcal nuclease digestion followed by rate zonal **sucrose** sedimentation. Most of the infectivity in the gradient (84%) had a characteristic mean size of approximately 120S, and was resolved from 70% of a host glycoprotein (**PrP**) that can cosediment with infectivity. In infectious size fractions, nucleic acids were reduced approximately one million-fold with respect to starting brain homogenate, and specific purification of infectivity was approximately 100,000-fold with respect to nucleic acid. Using a novel polymerase chain reaction strategy, we were able to amplify RNA species in these fractions.
Remarkably, host polyadenylated sequences of 1 to over 4 kb were detected in the nuclease-protected infectious fractions. These strategies set the stage for the identification of similar nucleic acids that may be specific

Not in Lib

L7 ANSWER 14 OF 14 MEDLINE
TI Molecular characteristics of the major scrapie prion protein.
AU Bolton D C; McKinley M P; Prusiner S B
SO BIOCHEMISTRY, (1984 Dec 4) 23 (25) 5898-906.
Journal code: A0G. ISSN: 0006-2960.
AB A major protein was identified that purifies with the scrapie agent extracted from infected hamster brains. The protein, designated **PrP** 27-30, was differentiated from other proteins in purified fractions containing the scrapie agent by its microheterogeneity (Mr 27000-30000) and its unusual resistance to protease digestion. **PrP** 27-30 was found in all fractions enriched for scrapie prions by discontinuous **sucrose** gradient sedimentation or sodium dodecyl sarcosinate-agarose gel electrophoresis. It is unlikely that **PrP** 27-30 is a pathologic product because it was found in fractions isolated from the brains of hamsters sacrificed prior to the appearance of histopathology. If **PrP** 27-30 is present in normal brain, its concentration must be 100-fold lower than that found in equivalent fractions from scrapie-infected hamsters. Three protease-resistant proteins similar to **PrP** 27-30 were found in fractions obtained by discontinuous **sucrose** gradient sedimentation of scrapie-infected mouse brain. These proteins were not evident in corresponding fractions prepared from normal mouse brain. One-dimensional peptide maps comparing **PrP** 27-30 and normal hamster brain proteins of similar molecular weight demonstrated that **PrP** 27-30 has a primary structure which is distinct from these normal proteins. Heating substantially purified scrapie fractions to 100 degrees C in sodium dodecyl sulfate inactivated the prion and rendered **PrP** 27-30 susceptible to protease digestion. Though the scrapie agent appears to be hydrophobic, **PrP** 27-30 remained in the aqueous phase after extraction with organic solvents, indicating that it is probably not a proteolipid. **PrP** 27-30 is the first structural component of the scrapie prion to be identified.

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MS-8209, a water-soluble amphotericin B derivative, affects both scrapie agent replication and PrPres accumulation in Syrian hamster scrapie.
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Sensitive enzyme-linked immunosorbent assay for detection of PrP(Sc) in crude tissue extracts from scrapie-affected mice.

Grathwohl KU, Horiuchi M, Ishiguro N, Shinagawa M

Department of Veterinary Public Health, Obihiro University of Agriculture and Veterinary Medicine, Hokkaido, Japan.

An enzyme-linked immunosorbent assay (ELISA) was developed that detects PrP(Sc) in crude extracts from brain and spleen tissue of scrapie-affected mice with high sensitivity and specificity. Brain tissue was homogenized in 8% Zwittergent 3-12 and 0.5% Sarkosyl. The homogenate was treated with collagenase and DNase I and then subjected to proteinase K digestion. Precipitates containing PrP(Sc) were obtained by ultracentrifugation. Spleen tissue was homogenized in 4% Triton X-100 and 0.5% Sarkosyl, and the homogenate was treated firstly with collagenase and DNase I, and secondly with proteinase K. PrP(Sc) was then extracted with 6.25% Sarkosyl and precipitated through salting-out with NaCl and by ultracentrifugation. When PrP(Sc) was dissolved in 3-4 M guanidine thiocyanate and adsorbed to microtiter plates, strong and specific reactions to the formation of antigen-antibody complexes could be detected by ELISA. The sensitivity of PrP(Sc)-detection for this ELISA, as measured by serial dilution of scrapie material in tissue homogenates from uninfected animals, was equal or higher than that attained by Western blot. This ELISA is more rapid than Western blot and seems to be more suitable for screening large numbers of animals. It also has potential application for the diagnosis of the transmissible spongiform encephalopathies.

PMID: 9079766, UI: 97234492

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Western blot mapping of disease-specific amyloid in various animal species and humans with transmissible spongiform encephalopathies using a high-yield purification method.

Beekes M, Baldauf E, Cassens S, Diringer H, Keyes P, Scott AC, Wells GA, Brown P, Gibbs CJ Jr, Gajdusek DC

Robert Koch-Institut, Bundesinstitut fur Infektionskrankheiten und nicht ubertragbare Krankheiten, Berlin, Germany.

SAF-protein, an amyloid, is the main constituent of scrapie-associated fibrils (SAF) and a specific marker for transmissible spongiform encephalopathies (TSE). Using an improved extraction method and Western blot detection, the disease-specific amyloid was found in various parts of the central nervous system of hamsters orally infected with scrapie, of squirrel monkeys orally infected with kuru, sporadic Creutzfeldt-Jakob disease (CJD) and scrapie, of human patients with sporadic CJD, of a sheep with natural scrapie and of a cow with bovine spongiform encephalopathy (BSE). In human CJD samples, the concentration of TSE-specific amyloid was estimated to be 1000- to 10 000-fold lower than in the central nervous system of hamsters with scrapie. The extraction method has a yield of 70% and allows Western blot detection of the TSE-specific amyloid in samples representing 1-10 micrograms of brain tissue from intracerebrally infected hamsters, as well as in individual spleens from hamsters with terminal scrapie infected by the intracerebral, oral or intraperitoneal route. A 20-100 mg sample of material is sufficient for the extraction of the pathological protein from different rodent, monkey, ovine, bovine and human tissues. The results reported here demonstrate the potential suitability of the method for the routine diagnosis of TSE as well as for the detailed analysis of distribution patterns of the TSE-specific amyloid in experimental approaches to the investigation of these diseases.

PMID: 7595360, UI: 96030866

1 : *J Gen Virol* 1987 Jan;68 (Pt 1):225-31 Related Articles, Books

Effects of different methods of purification on aggregation of scrapie infectivity.

Castle BE, Dees C, German TL, Marsh RF

High levels of scrapie infectivity were found in detergent-insoluble residues of hamster brain purified by either repeated pelleting in 10% NaCl or by separation in Nycodenz gradients. Titres determined by the method of incubation interval assay were 100-fold higher than titres measured by endpoint dilution assay. The protein profiles and end-labelled RNA examined by one-dimensional polyacrylamide gel electrophoresis were not different from samples prepared from uninfected brain. Preparations produced by repeated pelleting were treated with RNase A and/or 7 M-urea with no loss of scrapie infectivity. However, the infectivity of samples prepared by gradient centrifugation in Nycodenz were reduced by 2 to 3 log10 LD50 by treatment with RNase A alone but not in combination with SDS. These results suggest that the scrapie agent may be aggregated by methods of purification employing pelleting in high concentrations of salt, or by adding polycations to disaggregated samples.

PMID: 3100716, UI: 87111462

1 : *J Gen Virol* 1994 Sep;75 (Pt 9):2499-503 Related Articles, Books, LinkOut

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Pharmacological studies of a new derivative of amphotericin B, MS-8209, in mouse and hamster scrapie.

Demaimay R, Adjou K, Lasmezas C, Lazarini F, Cherifi K, Seman M, Deslys JP, Dormont D

Laboratoire de Neuropathologie Experimentale et Neurovirologie, CEA/DSV/DPTE/SSA, Fontenay aux Roses, France.

Transmissible subacute spongiform encephalopathies (TSSE) are neurodegenerative diseases characterized by the presence of a modified, partially proteinase-resistant host protein, PrPSc, which accumulates in the brains of infected individuals. Recently it has been reported that amphotericin B (AmB) treatment of hamsters infected with scrapie strain 263K prolongs the incubation period of the disease, and dissociates in vivo replication of the scrapie agent from PrPSc accumulation. We report here on data obtained after treatment with AmB and one of its derivatives, MS-8209, in experimental scrapie of mouse and hamster. Treatment was carried out by the intraperitoneal route 6 days per week, at three different dosages initiated at the time of infection. Two regimens were used: during the early time of infection or throughout the experimental infection. Results indicate that MS-8209 was as efficient as AmB in prolonging the incubation time and decreasing PrPSc accumulation in the hamster scrapie model. A dose-dependent response was observed in mice treated early after experimental infection. At a dose of 2.5 mg/kg, MS-8209 significantly prolonged the incubation period (by 11.9%). In long-term treatment of mice, MS-8209 and AmB markedly reduced PrPSc levels in the preclinical stage of the disease. These data demonstrate that the effect of AmB is not restricted to one model (hamster-263K). This regimen leads to an inversion of the PrPSc to proteinase-sensitive protein (PrPSens) ratio, suggesting PrPSens (presumably cellular PrPC) accumulation occurs before its conversion into PrPSc. As it has been shown that AmB does not modify the infectivity titre, we conclude that the drugs could act by inhibiting either the interaction of the scrapie agent with PrPSens during the early times of infection or the conversion of PrPSens into PrPSc.

PMID: 7915757, UI: 94358757

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Scrapie prion rod formation in vitro requires both detergent extraction and limited proteolysis.

McKinley MP, Meyer RK, Kenaga L, Rahbar F, Cotter R, Serban A, Prusiner SB

Department of Neurology, University of California, San Francisco 94143.

Scrapie prion infectivity can be enriched from hamster brain homogenates by using limited proteolysis and detergent extraction. Purified fractions contain both scrapie infectivity and the protein PrP 27-30, which is aggregated in the form of prion rods. During purification, PrP 27-30 is produced from a larger membrane protein, PrPSc, by limited proteolysis with proteinase K. Brain homogenates from scrapie-infected hamsters do not contain prion rods prior to exposure to detergents and proteases. To determine whether both detergent extraction and limited proteolysis are required for the formation of prion rods, microsomal membranes were prepared from infected brains in the presence of protease inhibitors. The isolated membranes were then detergent extracted as well as protease digested to evaluate the effects of these treatments on the formation of prion rods. Neither detergent (2% Sarkosyl) extraction nor limited proteinase K digestion of scrapie microsomes produced recognizable prion amyloid rods. Only after combining detergent extraction with limited proteolysis were numerous prion rods observed. Rod formation was influenced by the protease concentration, the specificity of the protease, and the duration of digestion. Rod formation also depended upon the detergent; some combinations of protease and detergent did not produce prion amyloid rods. Similar results were obtained with purified PrPSc fractions prepared by repeated detergent extractions in the presence of protease inhibitors. These fractions contained amorphous structures but not rods; however, prion rods were produced upon conversion of PrPSc to PrP 27-30 by limited proteolysis. We conclude that the formation of prion amyloid rods in vitro requires both detergent extraction and limited proteolysis. In vivo, amyloid filaments found in the brains of animals with scrapie resemble prion rods in their width and their labeling with prion protein (PrP) antisera; however, filaments are typically longer than rods. Whether limited proteolysis and some process equivalent to detergent extraction are required for amyloid filament formation in vivo remains to be established.

PMID: 1704926, UI: 91140725

1 : *Antimicrob Agents Chemother* 1995 Dec;39(12):2810-2

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MS-8209, a new amphotericin B derivative, provides enhanced efficacy in delaying hamster scrapie.

Adjou KT, Demaimay R, Lasmezas C, Deslys JP, Seman M, Dormont D

Department de la Recherche Medicale, Commissariat a l'Energie Atomique, Fontenay aux Roses, Paris, France.

To test the efficacy of a new amphotericin B derivative, MS-8209, in delaying scrapie, hamsters were infected intracerebrally with the 263K scrapie agent and treated with MS-8209 either early in the course of the disease or continuously. The results show that (i) all treatments lengthened the incubation period of hamster scrapie, (ii) continuous treatment with MS-8209 doubled the length of the incubation period compared with that observed in infected, untreated animals, and (iii) all treatments delayed the accumulation of a proteinase-resistant prion protein and glial fibrillary acidic protein in the brain. These findings suggest that MS-8209 is a powerful tool for investigating the pathogenesis of transmissible subacute spongiform encephalopathies.

PMID: 8593027, UI: 96161306

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Differential effects of a new amphotericin B derivative, MS-8209, on mouse BSE and scrapie: implications for the mechanism of action of polyene antibiotics.

Adjou KT, Demaimay R, Lasmezas CI, Seman M, Deslys JP, Dormont D

Department de Recherche Medicale, Commissariat a l'Energie Atomique, Fontenay-aux-Roses, France.

Mice were infected intracerebrally with the bovine spongiform encephalopathy (BSE) or the scrapie agent and treated during 8 weeks postinfection to test the protective effect of a new amphotericin B (AmB) derivative, MS-8209, in experimental transmissible spongiform encephalopathies. The results show that (i) the treatment prolonged the incubation period of both BSE-infected and scrapie-infected mice, (ii) MS-8209 and AmB were much more efficient in delaying the onset of scrapie than that of BSE, and (iii) a delay in Prp-res (proteinase K-resistant prion protein) and GFAP (glial fibrillary acidic protein) accumulation was observed in the brains of scrapie-infected mice, but was not significant in BSE-infected mice. The analysis of the molecular and clinical results strongly suggests a common mechanism of action of this category of drugs on the different transmissible spongiform encephalopathy strains. This could be due to an interaction with the PrP transconformation process leading to the formation of PrP-res.

PMID: 8837228, UI: 96434249

1 : *Ann N Y Acad Sci* 1994 Jun 6;724:259-81 Related Articles, Books, LinkOut

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Dementias, neurodegeneration, and viral mechanisms of disease from the perspective of human transmissible encephalopathies.

Manuelidis L

Section of Neuropathology, Yale University Medical School, New Haven, Connecticut 06510.

Related Resources

Our transmission experiments with human CJD emphasize the centrality of an exogenous infectious pathogen that can exist in symbiosis with its host for extended periods. Many latent or persistent viruses can cause neurodegenerative disease and may have a role in late onset dementias. There are reasons to believe that CJD infections may share properties with some of these latent viruses in causing dementia, and several retroviral mechanisms may be operative in CJD. In order to clarify viral-like attributes of the CJD agent we have closely followed infectivity and find the following: 1) the CJD agent has a virus-like size and density, and is biochemically separable from most host-encoded prion protein (PrP); 2) Endogenous retroviral IAP RNA sequences of 5,000 bases, as well as several gag-like nucleic acid binding proteins, co-purify with infectivity in preparations treated with high concentrations of anionic detergents and exhaustive nuclease digestion. They signify the purification of true viral cores rather than aggregation artifacts, and diminish claims that there are no protected nucleic acids of > 50 bases in highly purified infectious preparations; 3) In established hamster CJD, temporal studies show the agent has an effective doubling time of approximately 7.5 days in brain, consistent with complex host-viral interactions common to slow viral infections; 4) PrP-res does not correspond to titered levels of infectivity either in a biochemical or an in vivo setting but may function as a viral receptor that can modulate disease expression. Interestingly, functional changes in glial cells occur earlier than PrP-res changes, and indicate an important role for glial cells in evolving infections; 5) Human-rodent transmission studies suggest that CJD, or a CJD-like variant can be a common but latent infection of humans, with relatively infrequent expression of neurological disease. Susceptibility to disease can rest on host attributes and possibly age-related co-factors. Nonetheless, fundamental viral principles are also operative. Agent strain variants, viral burden, and the routes of infection are critical parameters for latency and disease expression. The properties described above have led me to return to the inclusion of CJD (and scrapie) in the panorama of conventional slow viral infections of the brain, as originally proposed by Sigurdsson. Identification of virus-specific molecules are essential for elucidating the role of these agents in the spectrum of human dementias.

1 : *Biosci Rep* 1986 May;6(5):459-65

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Scrapie-associated fibrils (SAF) purification method yields amyloid proteins from systemic and cerebral amyloidosis.

Kitamoto T, Hikita K, Tashima T, Tateishi J, Sato Y

We identified fibrils from non-transmissible systemic and cerebral amyloidosis using the purification method of scrapie-associated fibrils (SAF). The fibrils possessed the same nature of congophilia, filamentous structures and molecular weights as amyloid fibrils, and were resistant to Proteinase K digestion. This SAF method makes for a rapid extraction from amyloid-laden tissues. The method, therefore, may purify nontransmissible amyloids alone or together with SAF proteins.

PMID: 2874846, UI: 86297037

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1 : *FEMS Microbiol Immunol* 1992 Jul;4(5):235-42 Related Articles, Books, LinkOut

The infectivity of spongiform encephalopathies: does a modified membrane hypothesis account for lack of immune response?

Alper T

Birkholt, Southampton, UK.

Scrapie, the prototype of a group of diseases which have the unique property of being both hereditary and infectious, is also exceptional in that it fails to evoke an immune response. Purification of crude scrapie preparations revealed a strong association of infectivity with a membrane protein ('PrPsc'); but a protein with the same amino acid sequence ('PrPc') was subsequently also found in normal mammalian nervous tissue. It is postulated by some investigators that 'PrPsc' is itself the infectious agent, or the most important part thereof, but in papers making that proposal immunological aspects have not been addressed. Experimental evidence supporting the hypothesis of a membrane fragment as agent has likewise lately not been taken into account. A modified form of the membrane hypothesis could account for immunological as well as genetic aspects of these diseases.

Publication Types:

- Review
- Review, tutorial

PMID: 1355344, UI: 92385087

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1 : *J Infect Dis* 1989 Nov;160(5):795-802 Related Articles, Books, LinkOut

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Published erratum appears in J Infect Dis 1990 Mar;161(3):591

Amphotericin B: a novel class of antiscrapie drugs.

Pocchiari M, Casaccia P, Ladogana A

Department of Biology, University of Lecce, Italy.

Related Resources

Amphotericin B (AmB) has been able to lengthen the incubation period of intracerebrally (ic) scrapie-injected hamsters to 45 d. This article reports a linear relationship between AmB doses and the duration of the incubation periods of ic-treated animals compared with controls, a greater effect of AmB treatment administered 2 w before or the same day of ic scrapie incubation, and the ineffectiveness of mepartricin, an AmB analogue, in prolonging the incubation period of ic scrapie-injected hamsters. The beneficial effect of AmB appears due to a delay in the replication of the scrapie agent in the brain of infected hamsters. Moreover, AmB suppresses scrapie replication in the spleen of treated animals. Three hypotheses may explain these results: (1) AmB alters a hypothetical scrapie receptor, preventing the entry of the agent into central nervous system (CNS) target cells; (2) AmB interferes with mechanisms involved in scrapie replication; (3) AmB prevents the formation and accumulation of a scrapie-specific amyloid protein responsible for the disease. Whatever the mechanism of action, AmB is the only currently available drug to modify experimental CNS scrapie infection, so AmB is proposed as a novel class of antiscrapie drugs.

PMID: 2509571, UI: 90038632

1 : *Arch Virol* 1990;112(1-2):103-14 Related Articles, Books, LinkOut

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Intraperitoneal infection with scrapie is established within minutes of injection and is non-specifically enhanced by a variety of different drugs.

Kimberlin RH, Walker CA

Institute for Animal Health, AFRC & MRC Neuropathogenesis Unit, Edinburgh, Scotland.

Single intraperitoneal (i.p.) doses of 16 different drugs were given to mice 2 h before injecting scrapie i.p. Scrapie was injected as serial ten-fold dilutions of standard inocula and the effective titres obtained were used as a measure of the relative efficiency of infection in treated compared to saline injected mice. Despite the wide variety of drugs tested, most of them increased, non-specifically, the efficiency of infection by 0.6 to 2.1 log10 i.p. LD50 units (i.e., 4 to 126-fold), but only when both drug and scrapie were given i.p. The effect was greatest with a 2 h or a 6 h interval suggesting an involvement either of resident peritoneal cells or of elicited cells such as polymorphonuclear neutrophils. There was no increase in the efficiency of infection after intervals of 2 or 7 days when induced macrophages would predominant. The reverse sequence of injections (scrapie-0.5 h-drug) had no effect despite the persistence of high scrapie titre in the peritoneum at the time of drug injection. However, the effect was restored by a second injection of scrapie in the sequence, scrapie-drug-scrapie. It is concluded that scrapie infection is established within minutes of injection but much of the inoculum is associated with peritoneal cells which are irrelevant to pathogenesis. Drugs may enhance the infection of relevant peritoneal cells or their targeting to the visceral lymphoreticular tissues where early replication takes place.

PMID: 2142415, UI: 90314791

1 : *Antimicrob Agents Chemother* 1991 Jul;35(7):1486-8 Related Articles, Books, LinkOut

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Measurement of the concentration of amphotericin B in brain tissue of scrapie-infected hamsters with a simple and sensitive method.

Casaccia P, Ladogana A, Xi YG, Ingrosso L, Pocchiari M, Silvestrini MC, Cittadini A

Institute of General Pathology, Catholic University, Rome, Italy.

Related Resources

A simple, sensitive, and reproducible assay for the measurement of the amphotericin B concentration in tissue extracts was developed by using the fourth derivative of the absorption spectrum of amphotericin B between wavelengths of 330 and 430 nm. The amphotericin B concentration in spleen and brain was proportional to the total amount administered. The amphotericin B concentration in the brain was highly correlated with the increase in the mean incubation period of intracerebrally scrapie-infected hamsters.

PMID: 1929313, UI: 92027635

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1 : *J Virol* 1999 Apr;73(4):3511-3

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FREE Journal of Virology

Effectiveness of polyene antibiotics in treatment of transmissible spongiform encephalopathy in transgenic mice expressing Syrian hamster PrP only in neurons.

Demaimay R, Race R, Chesebro B

Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, Montana 59840, USA.

To date very few drugs have favorably influenced the course of transmissible spongiform encephalopathies. In previous studies, the polyene antibiotics amphotericin B (AmB) and MS-8209 prolonged the incubation time in Syrian hamsters of the 263K strain of scrapie, but AmB had no effect against other scrapie strains in Syrian hamsters. In the present experiments using transgenic mice expressing Syrian hamster PrP in neurons only, MS-8209 extended the life spans of animals infected with the 263K strain but not the DY strain. AmB was effective against both 263K and DY and prevented death in 18% of DY-infected animals. The AmB effect against strain 263K was more prominent in mice whose endogenous PrP gene had been inactivated by homologous recombination. It was unclear whether this difference was due to a change in the duration of the disease or to possible interactive effects between the mouse PrP gene and the drugs themselves. The effectiveness of treatment after intracerebral scrapie infection in transgenic mice expressing PrP only in neurons suggested that neurons are important sites of action for these drugs.

PMID: 10074211, UI: 99174058

1 : *J Gen Virol* 1977 Feb;34(2):295-304 Related Articles, Books, LinkOut

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Characteristics of a short incubation model of scrapie in the golden hamster.

Kimberlin RH, Walker C

Repeated passage of the "Chandler" strain of scrapie in female golden hamsters using the intracerebral route of inoculation reduces the minimum incubation period to 60 days, about half of the minimum incubation period so far found in any of the mouse models of scrapie. The infectivity titres in brain in the clinical stage of the disease are considerably higher (greater than 8-0 -log10 LD50 i.c. units/0-05 g) than those found in mouse scrapie. The biological characteristics of this model of hamster scrapie are reported, including the effects on incubation period of route of inoculation, dose of agent, sex of hamster, ambient temperature (hibernation) and splenectomy. Some general and specific applications of this experimental model of scrapie are discussed.

PMID: 402439, UI: 77120346

1 : *J Gen Virol* 1979 Jan;42(1):107-17

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Pathogenesis of scrapie: agent multiplication in brain at the first and second passage of hamster scrapie in mice.

Kimberlin RH, Walker CA

The intracerebral (i.c.) injection of mice with a particular source of hamster passaged scrapie produced disease after an incubation period of 325 +/- 6 days (mean +/- s.e.). The incubation period at the second i.e. passage in mice was reduced to 149 +/- 2 days. Studies were made of the dynamics of agent replication at 1st and 2nd passages in mice. At first passage, there was a 'zero phase' lasting about 175 days, when no infectious agent was detected in brain (or spleen), followed by a period of agent replication which lasted 150 days. At second passage, there was no significant 'zero phase' and agent replication occupied the whole of the incubation period. The occurrence of a 'zero phase' on interspecies passage of scrapie is discussed in relation to other reports of a 'zero phase' in mouse passaged scrapie.

PMID: 103999, UI: 79090118

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Experimental drug treatment of scrapie: a pathogenetic basis for rationale therapeutics.

Pocchiari M, Salvatore M, Ladogana A, Ingrosso L, Xi YG, Cibati M, Masullo C

Department of Biology, University of Lecce, Italy.

Pharmacological treatment with polyanions or amphotericin B in hamsters with experimental scrapie reveals that it is possible to delay the appearance of the disease only when the drug is given before the invasion of the agent into the clinical target areas of the brain. We suggest such early treatment may be possible for individuals at high risk of acquiring the disease, such as healthy mutation-positive relatives of patients with familial Creutzfeldt-Jakob disease or Gerstmann-Straussler syndrome, or recipients of potentially contaminated pituitary-extracted human growth hormone.

Publication Types:

- Review
- Review, tutorial

PMID: 1761115, UI: 92104308

1 : *J Gen Virol* 1999 Apr;80 (Pt 4):1079-85 Related Articles, Books, LinkOut

J. General Virology

MS-8209, a water-soluble amphotericin B derivative, affects both scrapie agent replication and PrPres accumulation in Syrian hamster scrapie.

Adjou KT, Demaimay R, Deslys JP, Lasmezas CI, Beringue V, Demart S, Lamoury F, Seman M, Dormont D

CEA, Service de Neurovirologie, Fontenay aux Roses, France. ADJOU@dsvidf.cea.fr

Amphotericin B (AmB) has been shown to delay hamster scrapie. Infectivity studies have been performed previously using AmB in order to understand the relationship between the accumulation of an abnormal isoform (PrPres) of the prion protein and 263K scrapie agent replication in the brain. The first study reported that AmB had no effect upon agent replication, although it delayed the development of both clinical signs and PrPres accumulation. However, subsequent experiments using the same model showed a significant effect both on agent replication and PrPres accumulation early in infection. This fundamental discrepancy was assumed to be linked to differences in experimental protocols. In order to unravel the issue, a new experiment has been performed encompassing different protocols and using an AmB derivative, MS-8209, that can be used at higher doses because of its lower toxicity. The findings of this study exclude the suspected differences in the protocols as the reason for previous conflicting results, and suggest strongly that these discrepancies were due to a low dose of AmB causing a 'threshold effect'. Overall, this study indicates that, in this model, PrPres cannot be dissociated from infectivity by polyene antibiotics.

PMID: 10211979, UI: 99226961

1 : *J Virol* 1997 Dec;71(12):9685-9

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FREE Journal of Virology

Late treatment with polyene antibiotics can prolong the survival time of scrapie-infected animals.

Demaimay R, Adjou KT, Beringue V, Demart S, Lasmezas CI, Deslys JP, Seman M, Dormont D

Commissariat a l'Energie Atomique, Departement de Recherche Medicale, Service de Sante des Armees, Fontenay aux Roses, France. rdemaimay@atlas.niaid.nih.gov

Amphotericin B (AmB) is one of the few drugs able to prolong survival times in experimental scrapie and delays the accumulation of PrPres, a specific marker of this disease in the brain in vivo. Previous reports showed that the AmB effect is observed only if the drug is administered around the time of infection. In the present study, intracerebrally infected mice were treated with AmB or one of its derivatives, MS-8209, between 80 and 140 days postinoculation. We observed an increased incubation time and a delay in PrPres accumulation and glial fibrillary acidic protein gene expression. Treatment starting at 80 days postinoculation was as efficient as long-term treatment starting the day of inoculation. Our results indicate that polyene antibiotics may interfere, throughout the course of the experimental disease, with the propagation of the scrapie agent.

PMID: 9371634, UI: 98037685

Porphyrin and phthalocyanine antiscrapie compounds.

Priola SA, Raines A, Caughey WS

Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT 59840, USA. spriola@nih.gov

The transmissible spongiform encephalopathies (TSEs) are fatal, neurodegenerative diseases for which no effective treatments are available. The likelihood that a bovine form of TSE has crossed species barriers and infected humans underscores the urgent need to identify anti-TSE drugs. Certain cyclic tetrapyrroles (porphyrins and phthalocyanines) have recently been shown to inhibit the in vitro formation of PrP-res, a protease-resistant protein critical for TSE pathogenesis. We now report that treatment of TSE-infected animals with three such compounds increased survival time from 50 to 300%. The significant inhibition of TSE disease by structurally dissimilar tetrapyrroles identifies these compounds as anti-TSE drugs.

PMID: 10688802, UI: 20156774

The pathological changes in peripheral organs of scrapie-infected animals.

Ye X, Carp RI

New York State Institute for Basic Research in Developmental Disabilities, Staten Island, USA.

Scrapie is an unconventional neurodegenerative disease in sheep and goats that has been known in Europe for over 260 Years. The scrapie agents affect the brain and are transmissible from animal to animal. Key features of scrapie infections are abnormal behavior and deficits in motor function. These clinical findings can be related to the damage found in the central nervous system. In some scrapie strain-host model systems there are other manifestations of disease that appear to be related to pathological changes found in the peripheral organs, especially in the endocrine organs such as pituitary, adrenal glands, the islet of Langerhans and ovary. In those model systems in which extensive histopathological changes have been seen in peripheral organs, the titers of scrapie infectivity and the levels of the scrapie specific protein, PrPSc, are relatively low in the affected organs. These data suggest but do not prove that changes in peripheral organs are secondary to the scrapie-induced neurodegeneration that is occurring in the brain. In some scrapie strain-host combinations, obesity and aberrant glucose metabolism are seen in the preclinical and clinical phases of the incubation period. There appear to be two pathways that lead to these particular clinical manifestations. In SJL mice infected by the ME7 or 22L strains of mouse-adapted scrapie and in some scrapie-infected sheep, the mechanism is related to changes induced in the hypothalamic-pituitary-adrenal axis. The other pathway is exemplified by hamsters infected with two hamster-adapted scrapie strains, 139H and 22CH; it appears that lesions found in the hypothalamic-islets of Langerhans axis are critical. A number of reviews on the pathological changes in the central nervous system have been published and therefore, in this review article, we focus on the gross and histopathological changes in peripheral organs in several scrapie strain-host combinations. The changes induced in peripheral organs in a number of scrapie strain-host combinations expand the number of diseases in which the unconventional slow infections could serve as a model. Further work in this area could help us to understand the mechanisms and pathways of the pathological changes found in the peripheral organs of the scrapie-infected animals.

Publication Types:

- Review

1 : *J Gen Virol* 1987 Jan;68 (Pt 1):219-23 Related Articles, Books, LinkOut

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Amphotericin B delays the incubation period of scrapie in intracerebrally inoculated hamsters.

Pocchiari M, Schmittinger S, Masullo C

The scrapie-infected hamster has been considered an excellent model for the study of slow virus diseases of man (Creutzfeldt-Jakob disease) and animals. At the moment no therapy is available for the cure of these fatal central nervous system diseases, although several drugs have been tested. We found that amphotericin B (AmB), a polyene antibiotic, increased the incubation time of scrapie disease in animals infected by either the intraperitoneal or intracerebral route. Hamsters inoculated with a 10% brain suspension of the 263K strain of scrapie showed clinical signs of disease in 54.6 +/- 4.7 days. Under AmB treatment (1 mg/kg for 6 days a week) the incubation time increased with the length of treatment, up to a maximum delay of 45 days. AmB may interact with the scrapie agent on cell plasma membranes and may thereby decrease the rate of scrapie replication. However, AmB did not have any effect when administered after the clinical onset of scrapie disease.

PMID: 2433387, UI: 87111461

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1 : *J Comp Pathol* 2000 Jan;122(1):3-8 Related Articles, Books, LinkOut

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MS-8209, an amphotericin B analogue, delays the appearance of spongiosis, astrogliosis and PrPres accumulation in the brain of scrapie-infected hamsters.

Adjou KT, Privat N, Demart S, Deslys JP, Seman M, Hauw JJ, Dormont D

CEA, Service de Neurovirologie, DSV/DRM, CRSSA, B.P. 6, 60-68, Avenue du General Leclerc, 92 265 Fontenay aux Roses Cedex, France.

The histopathological response of scrapie-infected hamsters treated at the late stage of the infection with an "anti-scrapie" drug, a polyene macrolide antibiotic designated MS-8209, was evaluated in the brain. The results showed that (1) MS-8209 prolonged significantly the incubation time of the experimental disease, (2) MS-8209 delayed the appearance of spongiosis and astrogliosis in the brain, (3) immunodetection of abnormal prion protein and glial fibrillary acidic protein was significantly reduced in the central nervous system. In addition, this report indicates that polyene antibiotics markedly delay the development of the classical brain lesions that result from scrapie infection.

PMID: 10627386, UI: 20094860

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1 : *Protein Sci* 1993 Dec;2(12):2206-16 Related Articles, Books, LinkOut

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Thermal stability and conformational transitions of scrapie amyloid (prion) protein correlate with infectivity.

Safar J, Roller PP, Gajdusek DC, Gibbs CJ Jr

Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892.

Related Resources

The scrapie amyloid (prion) protein (PrP27-30) is the protease-resistant core of a larger precursor (PrPSc) and a component of the infectious scrapie agent; the potential to form amyloid is a result of posttranslational event or conformational abnormality. The conformation, heat stability, and solvent-induced conformational transitions of PrP27-30 were studied in the solid state in films by CD spectroscopy and correlated with the infectivity of rehydrated and equilibrated films. The exposure of PrP27-30 in films to 60 degrees C, 100 degrees C, and 132 degrees C for 30 min did not change the beta-sheet secondary structure; the infectivity slightly diminished at 132 degrees C and correlated with a decreased solubility of PrP27-30 in sodium dodecyl sulfate (SDS), probably due to cross-linking. Exposing PrP27-30 films to formic acid (FA), trifluoroacetic acid (TFA), trifluoroethanol (TFE), hexafluoro-2-propanol (HFIP), and SDS transformed the amide CD band, diminished the mean residue ellipticity of aromatic bands, and inactivated scrapie infectivity. The convex constraint algorithm (CAA) deconvolution of the CD spectra of the solvent-exposed and rehydrated solid state PrP27-30 identified five common spectral components. The loss of infectivity quantitatively correlated with a decreasing proportion of native, beta-pleated sheet-like secondary structure component, an increasing amount of alpha-helical component, and an increasingly disordered tertiary structure. The results demonstrate the unusual thermal stability of the beta-sheet secondary structure of PrP27-30 protein in the solid state. The conformational perturbations of PrP27-30 parallel the changes in infectivity and suggest that the beta-sheet structure plays a key role in the physical stability of scrapie amyloid and in the ability to propagate and replicate scrapie.

PMID: 7905316, UI: 94129403

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1 : *Crit Rev Biochem Mol Biol* 1991;26(5-6):397-438 Related Articles, Books, LinkOut

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Molecular biology and transgenetics of prion diseases.

Prusiner SB

Department of Neurology, University of California, San Francisco 94143.

Considerable progress has been made deciphering the role of an abnormal isoform of the prion protein (PrP) in scrapie of animals and Gerstmann-Straussler syndrome (GSS) of humans. Some transgenic (Tg) mouse (Mo) lines that carry and express a Syrian hamster (Ha) PrP gene developed scrapie 75 d after inoculation with Ha prions; non-Tg mice failed to show symptoms after greater than 500 d. Brains of these infected Tg(HaPrP) mice featured protease-resistant HaPrPSc, amyloid plaques characteristic for Ha scrapie, and 10(9) ID50 units of Ha-specific prions upon bioassay. Studies on Syrian, Armenian, and Chinese hamsters suggest that the domain of the PrP molecule between codons 100 and 120 controls both the length of the incubation time and the deposition of PrP in amyloid plaques. Ataxic GSS in families shows genetic linkage to a mutation in the PrP gene, leading to the substitution of Leu for Pro at codon 102. Discovery of a point mutation in the Prp gene from humans with GSS established that GSS is unique among human diseases--it is both genetic and infectious. These results have revised thinking about sporadic Creutzfeldt-Jakob disease, suggesting it may arise from a somatic mutation. These findings combined with those from many other studies assert that PrPSc is a component of the transmissible particle, and the PrP amino acid sequence controls the neuropathology and species specificity of prion infectivity. The precise mechanism of PrPSc formation remains to be established. Attempts to demonstrate a scrapie-specific nucleic acid within highly purified preparations of prions have been unrewarding to date. Whether transmissible prions are composed only of PrPSc molecules or do they also contain a second component such as small polynucleotide remains uncertain.

Publication Types:

- Review
- Review, academic

PMID: 1684745, UI: 92103927

Inactivation of SE agents.

Taylor DM

AFRC Neuropathogenesis Unit, Institute for Animal Health, Edinburgh, UK.

The transmissible agents of the spongiform encephalopathies are relatively resistant to inactivation, and accidental transmission has occurred in animals and man. Rigorous chemical or physical procedures are required to achieve decontamination, and their effectiveness can only be determined by bioassay in animals. The best-defined model is scrapie in mice or hamsters, and this has been used in many of the studies to establish practical inactivation procedures. Although a number of techniques had been considered to be effective, more recent observations suggest that some of these may not always be completely reliable. Research continues on scrapie inactivation, and work is in progress to extend this knowledge to the BSE agent.

Publication Types:

- Review
- Review, academic

PMID: 8137130, UI: 94184817

1 : *J Gen Virol* 1992 Mar;73 (Pt 3):661-5 Related Articles, Books, LinkOut

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Sulphate polyanions prolong the incubation period of scrapie-infected hamsters.

Ladogana A, Casaccia P, Ingrosso L, Cibati M, Salvatore M, Xi YG, Masullo C, Pocchiari M

Institute of General Pathology, Catholic University, Rome, Italy.

The effect of the organic sulphated polyanions, pentosan sulphate (SP54), dextran sulphate 500 (DS500) and suramin, have been tested on golden Syrian hamsters infected with the 263K strain of scrapie by the intraperitoneal (i.p.) or the intracerebral route. SP54 had the greatest effect in prolonging the incubation period of the disease when administered within 2 h of the i.p. inoculum. The same amount of SP54 given 24 h after scrapie inoculation had a potent effect in some animals and no effect in others. This result suggests that SP54 inhibits the uptake of the scrapie agent into the nerve endings and/or carrier cells at the site of the inoculum, i.e. the peritoneum, and that this event occurs in about 24 h. DS500 had a similar although less potent effect (22.4 days delay during the incubation period) than SP54 (54.4 days) when administered within 2 h of scrapie injection by the i.p. route, and suramin had only a minimal effect (10 days). This study suggests that treatment of scrapie and related spongiform encephalopathies of animals and man is possible only before the agent has reached the clinical target areas of the brain.

PMID: 1372039, UI: 92185477

1 : *Nature* 1992 Apr 16;356(6370):598-601 Related Articles, Books, LinkOut

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Amphotericin B treatment dissociates in vivo replication of the scrapie agent from PrP accumulation.

Xi YG, Ingrosso L, Ladogana A, Masullo C, Pocchiari M

Istituto di Patologia Generale, Universita Cattolica S, Cuore, Rome, Italy.

Scrapie and related animal and human disorders are neurodegenerative diseases characterized by the formation of a modified, partly proteinase-resistant protein (PrP) of the host, which tends to aggregate as amyloid fibrils and accumulate in the brain of infected individuals. There is a general consensus that the pathological form of PrP (PrPSc) is essential for the clinical appearance of the disease, but whether it is part of the scrapie agent or a by-product of viral infection is still controversial. Here we report that treatment of scrapie-infected hamsters with amphotericin B delays the accumulation in the brain of the proteinase-resistant portion of PrPSc by about 30 days without affecting scrapie replication. The consequence is that hamsters treated with amphotericin B developed clinical signs of disease later than infected controls. We argue that the proteinase-resistant portion of PrPSc is necessary for the development of the disease but that it is unlikely to be essential for scrapie replication.

Comments:

- Comment in: Nature 1992 Apr 16;356(6370):560

PMID: 1348570, UI: 92220188

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